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RADIOTERAPIA OGGI E DOMANI, 20 ANNI DELLA U.O.C. DI RADIOTERAPIA DELL'OSPEDALE MANZONI – LECCO

Stato dell'arte, problematiche attuali e prospettive future nel trattamento di:

Neoplasie del Sistema Nervoso Centrale

Michela Buglione di Monale
Radioterapia – Università e Spedali Civili, Brescia

27 novembre 2021

Primary tumors

histology 2016 → 2020

glioblastoma; oligodendroglioma state of art

volumes; techniques; doses

questions without answers

the winning strategy?

Secondary tumors

diagnosis; prognosis

treatment: radiotherapy alone vs with drugs

techniques; doses; toxicity

questions without answers

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the winning

Brain metastases

Abstract

Background. To define efficacy and toxicity of Immunotherapy (IT) with stereotactic radiotherapy (SRT) including radiosurgery (RS) or hypofractionated SRT (HFSRT) for brain metastases (BM) from non-small cell lung cancer (NSCLC) in a multicentric retrospective study from AIRO (Italian Association of Radiotherapy and Clinical Oncology).

Methods. NSCLC patients with BM receiving SRT + IT and treated in 19 Italian centers were analyzed and compared with a control group of patients treated with exclusive SRT.

Results. One hundred patients treated with SRT + IT and 50 patients treated with SRT-alone were included. Patients receiving SRT + IT had a longer intracranial Local Progression-Free Survival (iLPFS) (propensity score-adjusted $P = .007$). Among patients who, at the diagnosis of BM, received IT and had also extracranial progression ($n = 24$), IT administration after SRT was shown to be related to a better overall survival (OS) ($P = .037$). A multivariate analysis, non-adenocarcinoma histology, KPS = 70 and use of HFSRT were associated with a significantly worse survival ($P = .019$, $P = .017$ and $P = .007$ respectively). Time interval between SRT and IT ≤7 days ($n = 90$) was shown to be related to a longer OS if compared to SRT-IT interval >7 days ($n = 10$) (propensity score-adjusted $P = .008$). The combined treatment was well tolerated. No significant difference in terms of radionecrosis between SRT + IT patients and SRT-alone patients was observed. The time interval between SRT and IT had no impact on the toxicity rate.

Conclusions. Combined SRT + IT was a safe approach, associated with a better iLPFS if compared to exclusive SRT.

Immunotherapy i
radiotherapy for non-small cell lung cancer brain metastases: results from a multicentric retrospective study on behalf of AIRO

Neuro-Oncology 23(10), 1750–1764, 2021 | doi:10.1093/neuonc/noab129

Primary tumors

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Primary tumors

Neuro-Oncology
22(8), 1073–1113, 2020 | doi:10.1093/neuonc/noaa106 | Advance Access date 24 April 2020

Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions

Primary tumors

Biology

Glioblastomas are thought to arise from neuroglial stem or progenitor cells and are characterized by molecular heterogeneity

but its clinical utility remains unclear.

ylation) identified 3 main glioblastoma subgroups, each enriched for specific somatic alterations. The proneural gene expression/receptor tyrosine kinase (*RTK*) I/LGm6 DNA methylation group is marked by cyclin-dependent (*CDK4*) and platelet derived growth factor alpha amplifications and is most common in relatively younger adults. The classical gene expression/classic-like/ RTK II DNA methylation group shows a high frequency of *EGFR* amplifications and homozygous loss of *CDKN2A/B*. The mesenchymal/mesenchymal-like subtype is enriched for tumors with neurofibromatosis type 1 (*NF1*) loss and increased tumor infiltration with macrophages. These 3

Neuro-Oncology
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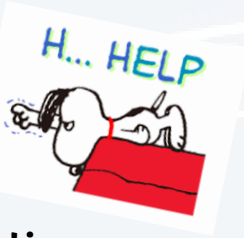
Primary tumors



Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy

Pathology and classification

The pathologic hallmarks of glioblastoma are:

- a diffusely infiltrative neoplasm with astroglial appearance (angulated nuclei and irregular chromatin),
- microvascular proliferation
- and/or necrosis

Third update of c-IMPACT-NOW recommend diagnostic criteria for "diffuse astrocytic gliomas, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV." → In the absence of IDH mutations, either TERT promoter mutations or EGFR amplification are now considered sufficient molecular evidence of glioblastoma with similar clinical outcome, even when histologic examination meets only WHO grade II or III criteria.

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Primary tumors

Pathology and classification

Conversely, mutations in IDH1/2 in adult diffuse gliomas allow prediction of extended patient survival.

In keeping with the distinct biology and clinical behavior of grade IV gliomas as a function of IDH mutation status, the cIMPACT-NOW consensus group suggests that the term “glioblastoma” no longer apply to IDH-mutant tumors, and suggests instead the term “astrocytoma, IDH-mutant, WHO grade IV” for such tumors, to distinguish them from IDH-wt glioblastoma

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Primary tumors

NEW

Pathology and classification → 2021

In the updated fourth edition CNS classification from 2016, the common diffuse gliomas of adults were divided into 15 entities, largely because different grades were assigned to different entities

WHO CNS5, on the other hand, includes only 3 types:
1 - Astrocytoma, IDH-mutant
2 - Oligodendroglioma, IDH-mutant and 1p/19q-codeleted;
3 - Glioblastoma, IDH-wildtype.

Neuro-Oncology
23(8), 1231–1251, 2021 | doi:10.1093/neuonc/noab106 | Advance Access date 29 June 2021

The 2021 WHO Classification of Tumors of the Central Nervous System: a summary

Table 1 2021 WHO Classification of Tumors of the Central Nervous System. Provisional Entities are in Italics

World Health Organization Classification of Tumors of the Central Nervous System, fifth edition
Gliomas, glioneuronal tumors, and neuronal tumors
Adult-type diffuse gliomas
Astrocytoma, IDH-mutant
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted
Glioblastoma, IDH-wildtype

Primary tumors

In the current classification all IDH-mutant diffuse astrocytic tumors are considered a single type (Astrocytoma, IDH-mutant) and are then graded as CNS WHO grade 2, 3, or 4.

- As a result, Glioblastoma, IDH-wildtype should be diagnosed in the setting of an IDH-wildtype diffuse and astrocytic glioma in adults if there is microvascular proliferation or necrosis or TERT promoter mutation or EGFR gene amplification or +7/–10 chromosome copy number changes.

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The 2021 WHO Classification of Tumors of the Central Nervous System: a summary

Primary tumors

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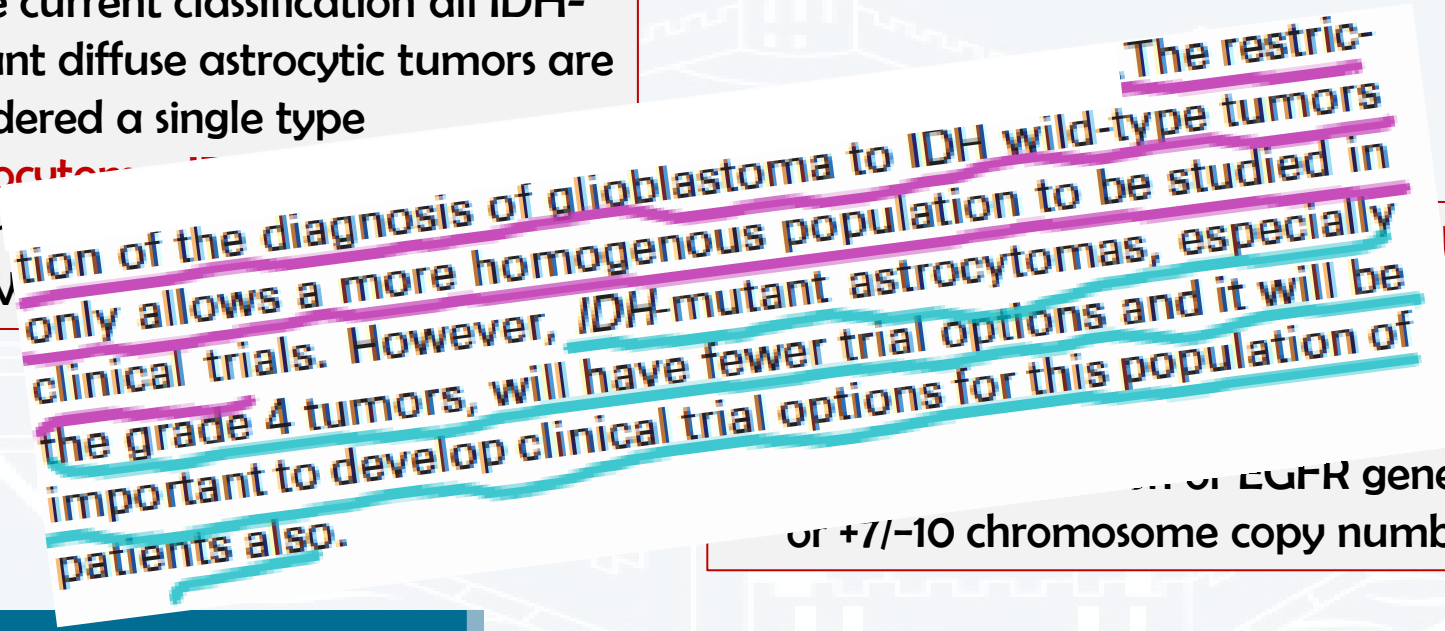

tion of the diagnosis of glioblastoma to IDH wild-type tumors only allows a more homogenous population to be studied in clinical trials. However, *IDH*-mutant astrocytomas, especially the grade 4 tumors, will have fewer trial options and it will be important to develop clinical trial options for this population of patients also.

The restric-

…ldtype should …IDH-wildtype …lults if there is …osis or TERT …n of EGFR gene amplification …or +7/–10 chromosome copy number changes.

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The 2021 WHO Classification of Tumors of the Central Nervous System: a summary

Primary tumors

Diagnosis and imaging

apparent diffusion coefficient (ADC)

cerebral blood volume (CBV)

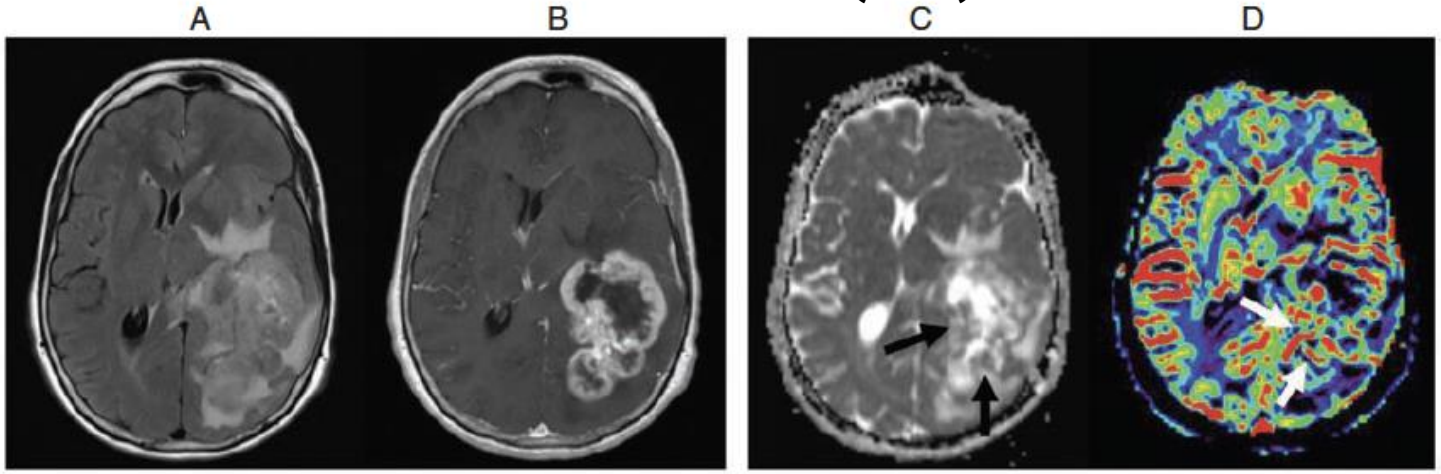

Fig. 4 Sixty-four-year-old with a glioblastoma who presented with word finding difficulty. FLAIR (A) and contrast-enhanced T1W (B) images show a large, necrotic-appearing, enhancing mass with surrounding T2/FLAIR signal abnormality in the periventricular regions. There is evidence of hypercellularity on ADC map (black arrow in C) and elevated blood volume on CBV map (white arrow in D)

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Primary tumors

Diagnosis and imaging

Accurate determination of response and progression remains a challenge.

- RANO criteria for highgrade gliomas is the most widely used standard in clinical trials.
- These criteria use 2D tumor measurements and provide guidance on evaluating pseudoresponse, non-enhancing progression, and pseudoprogression.
- More recently, modifications to the RANO criteria have been suggested using a post-RT baseline, and confirmation of progression on subsequent scans has been advised, especially for agents associated with pseudoprogression, to ensure that patients are not removed from therapies prematurely.
- Reduce the possibility that patients with spontaneously improving pseudoprogression would be offered salvage options or placed inappropriately on clinical trials for presumed progressive disease

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Primary tumors

Medical management and supportive care

dexamethasone

Corticosteroids, preferably dexamethasone (in conjunction with gastric protection if used at high doses), are given to reduce symptomatic peritumoral vasogenic edema.[96] Dexamethasone alleviates neurologic deficits and signs of increased intracranial pressure such as headache and drowsiness. Low doses (eg, 4 mg/day given in 1–2 doses) are effective in most clinically symptomatic patients without signs of herniation.[97,98] There is no need to give dexamethasone 4 times a day.[98] Side effects of dexamethasone worsen with increased dose and duration of treatment.[99,100] There is also growing evidence that corticosteroids may have an adverse effect on patient outcome, so they should be avoided if patients are not symptomatic.[101] Patients on chronic corticosteroids (≥20 mg prednisone equivalents daily for ≥1 month) should be considered for prophylaxis for osteoporosis and *pneumocystis jerovecii* pneumonia.[102]

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Primary tumors

Medical management and supportive care

Anti-epileptic drugs

course. While patients with seizures require anti-epileptic drugs (AEDs), studies have not clearly shown a benefit of prolonged primary AED prophylaxis in patients who have never had a seizure.[104,105] Current guidelines recommend tapering AEDs 1–2 weeks after surgery and avoiding long-term prophylaxis.[106] There is no role for primary perioperative prophylaxis

When AEDs are used, newer agents including levetiracetam and lacosamide are preferred over older drugs because of generally more favorable side effect profiles, reduced laboratory monitoring requirements, and lack of drug-drug interactions.[110] Emerging data suggesting that neurons and glioma cells form synapses via AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors raises the possibility that AEDs that inhibit these receptors, such as perampanel, may be beneficial not only in controlling seizures, but also through possible antiglioma activity.[111,112] However, a prior trial with another glutamate inhibitor, talampanel, was ultimately interpreted to be negative.[113]

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Primary tumors

Medical management and supportive care

Venous thromboembolism

Venous thromboembolism (VTE) risk is high in the perioperative period and persists well beyond, with one-year incidence of approximately 20%,[114,115] mandating a low threshold for pursuing diagnostic studies.[115] Most,[116,117] though not all,[118] studies suggest that the risk of precipitating intratumoral hemorrhage with anticoagulants is acceptably low, even in patients receiving bevacizumab.[119] The preferred anticoagulant is not well studied in brain tumors; in systemic cancer, low molecular weight heparin (LMWH) is preferred over warfarin.[120] Direct oral anticoagulants (DOACs) (factor Xa and thrombin inhibitors) have been reported to be safe in patients with brain tumors.[121] However, no randomized data are available for glioma patients and randomized trials on secondary prophylaxis of VTE with DOACs enrolling cancer patients have generally shown a similar or slightly higher efficacy than LMWH but with a slightly higher risk of bleeding.[122,123]

A high incidence of recurrent VTE with inferior vena cava (IVC) filters limits their use to patients with recent intracranial surgery, intratumoral hemorrhage, or absolute contraindications to anticoagulation.[110] Prophylaxis with anticoagulation outside of the perioperative setting has not been definitively studied, as the only trial addressing this issue was prematurely terminated for slow accrual.[124] A meta-analysis of pooled randomized clinical trial data indicated no survival benefit from anticoagulation in glioblastoma patients, but rather suggested that VTE should be treated more vigorously in this patient population.[125]

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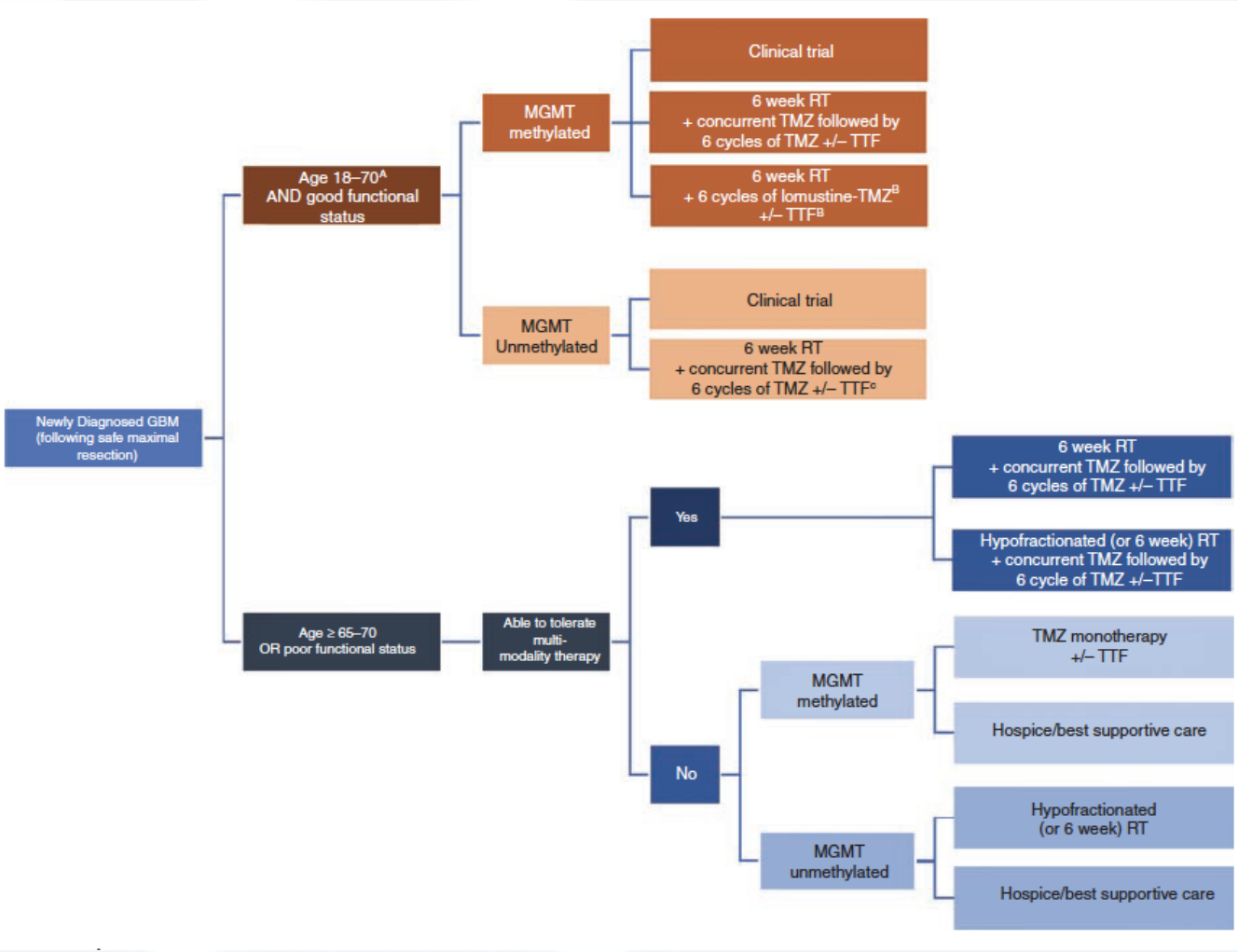
Primary tumors

Standard primary treatm



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Primary tumors

Radiotherapy target volumes

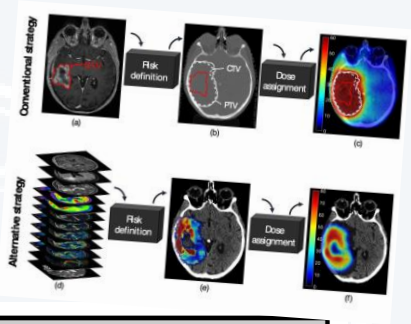

Table 2
Glioblastoma radiotherapy target volume delineation among cooperative groups

	ABTC	EORTC	NCCTG/Alliance	RTOG/NRG
One or 2 phase	Two-phase: 46 Gy → 14 Gy	One-phase 60 Gy	Two-phase: 50 Gy → 10 Gy	Two-phase: 46 Gy →14 Gy
Initial CTV	T2, T1-CE, cavity + 5 mm	T1-CE, cavity + 2–3 cm	T2, T1-CE, cavity + 2 cm to block edge	T2, T1-CE, cavity + 2 cm
Boost CTV	T1-CE, cavity + 5 mm	N/A	T1-CE, cavity + 2 cm to block edge	T1-CE, cavity + 2 cm
PTV	Generally 3–5 mm	Generally 5–7 mm	N/A	3–5 mm

Abbreviations: ABTC, adult brain tumor consortium; CE, contrast enhancement; CTV, clinical target volume; EORTC, European Organisation for Research and Treatment of Cancer; Gy, Gray; NCCTG, North Central Cancer Treatment Group; PTV, planning target volume; RTOG, Radiation Therapy Oncology Group.

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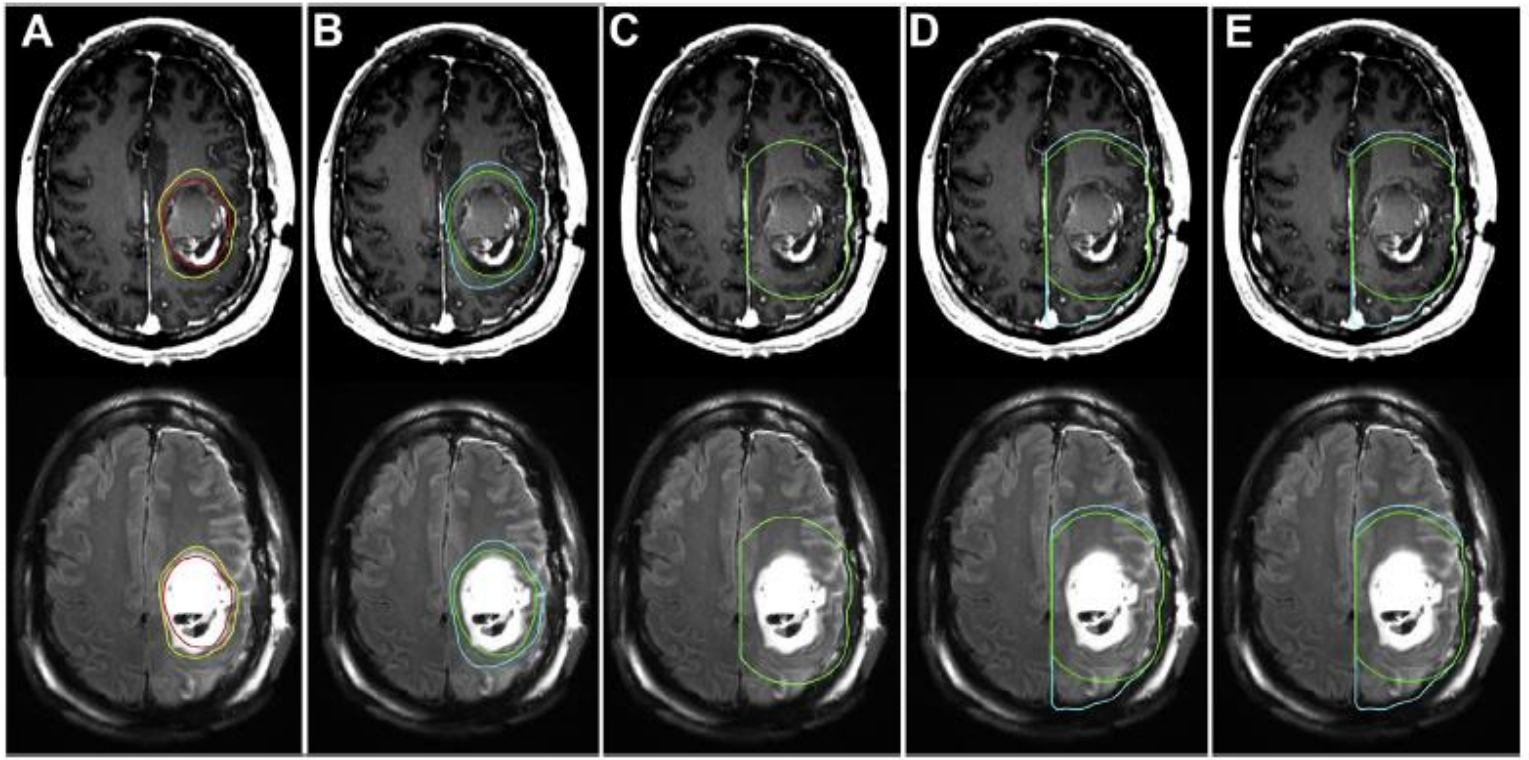

Fig. 1. Glioblastoma RT target volume delineation among different cooperative groups. Postoperative MRI T1 contrast-enhanced (*above*) and FLAIR (*below*) sequences. The gross tumor volume (GTV) initial is in yellow (97.73 cc) and GTV boost is in red (44.12 cc) (*A*). The ABTC volumes for clinical target volume (CTV) initial in cyan (46 Gy, 166.26 cc) and CTV boost in green (60 Gy, 81.83 cc) (*B*). The EORTC volume for the single phase CTV in green (60 Gy, 237.07 cc) (*C*). The NCCTG/Alliance volumes for CTV initial in cyan (50 Gy, 367.87 cc) and CTV boost in green (60 Gy, 237.07 cc) (*D*). The RTOG/NRG volumes for CTV initial in cyan (46 Gy, 367.87 cc) and CTV boost in green (60 Gy, 237.07 cc) (*E*).

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Neurosurg

Primary tumors

NEW

Radiotherapy target volumes – perspective

Identify and perform a model of GB infiltration

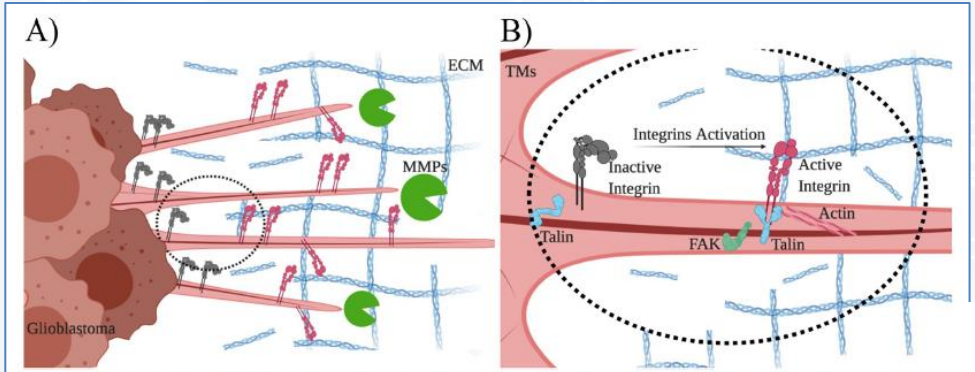
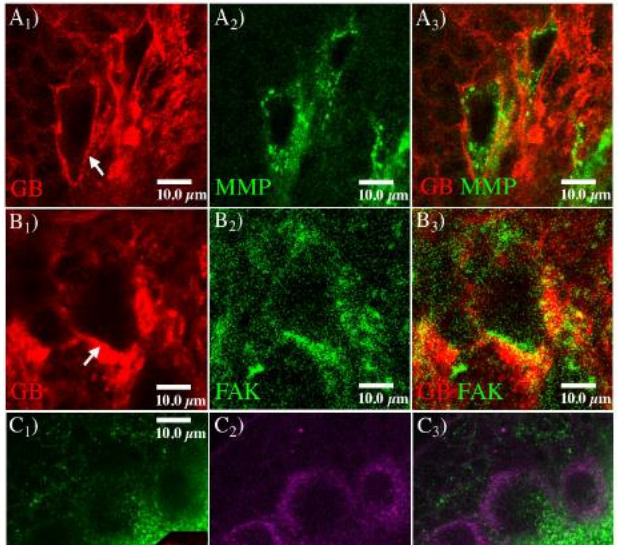


Fig 1. Diagram of GB and protein dynamics. Diagram of the interactions between the proteins involved in GB progression and that give rise to the mathematical model. A): GB cells produce and release in the extracellular space Matrix Metalloproteases (MMPs), which proteolyze the Extra Cellular Matrix (ECM) components. B): Magnification of Tumor Microtubes (TMs). Integrins are activated in the GB tumor microtubes upon interaction with ECM proteins. Active integrins, interacting with Actin filaments and the Talin adaptor protein, activate the Focal Adhesion Kinase (FAK) protein to promote cytoplasm dynamics.

https://doi.org/10.1371/journal.pcbi.1008632.g001



Therefore, any mathematical model that attempts to predict GB dynamics and reproduce the formation of these evolutionary patterns must face these challenges.

PLoS Comput Biol 2021; 17(1): e1008632.

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Identify and p

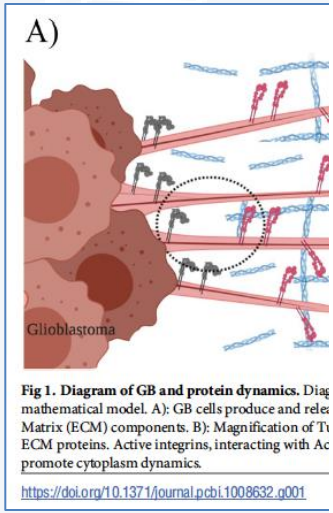

Fig 1. Diagram of GB and protein dynamics. Diag
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promote cytoplasm dynamics.

https://doi.org/10.1371/journal.pcbi.1008632.g001

- The mathematical model is based on a non-linear system of evolution equations in which the mechanisms leading chemotaxis, haptotaxis, and front dynamics compete with the movement induced by the saturated flux in porous media.

- This approach is able to capture the relative influences of the involved agents and reproduce the formation of patterns, which drive tumor front evolution.

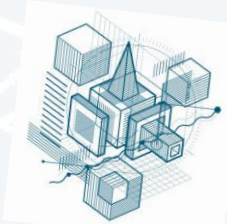
- These patterns have the value of providing biomarker information that is related to the direction of the dynamical evolution of the front and based on static measures of proteins in several tumor samples.

- Furthermore, we consider in our model biomechanical elements, like the tissue porosity, as indicators of the healthy tissue resistance to tumor progression

PLoS Comput Biol 2021; 17(1): e1008632.

Primary tumors

NEW



Radiotherapy target volumes – perspective

Different types of imaging

Dynamic CE MRI analyzes relative cerebral blood volume, cerebral blood flow, and vascular permeability. Together with diffusion weighted MRI, a surrogate for tumor cellularity these images can be integrated into a multiparametric imaging signature

3 different advanced imaging strategies seeking to redefine target delineation for glioblastoma:

- multiparametric magnetic resonance (MR),
- MR spectroscopy
- functional imaging.

A multi-institutional phase II trial (NCT02805179) → if multiparametric advanced imaging approach to guide RT (75 Gy/30#) → OS.

- first 12 patients → advanced imaging target 2 times smaller than the T1 enhancement volumes and 10 times smaller than the FLAIR volumes, with only a 57% overlap with the enhancement region on MRI alone

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Primary tumors

Radiotherapy target volumes – perspective

Different types of imaging

3 different advanced imaging strategies seeking to redefine target delineation for glioblastoma:

- multiparametric magnetic resonance (MR),
- MR spectroscopy
- functional imaging

Spectroscopic MRI (sMRI) to evaluate the regions of the brain with elevated cholineto-N-acetylaspartate ratio and guide dose escalation to these areas of elevated tumor related metabolic activity, which also correspond to the areas at risk for disease relapse

Integration of a dose-escalation (75 Gy/30 #) approach to sMRI-defined high-risk regions has been successfully tested;
- A phase II multiinstitutional pilot study using sMRI-defined target volumes (NCT03137888) is also under way with co-primary endpoints of feasibility and incidence of adverse events; data from the first 18 patients have been promising

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Primary tumors

Radiotherapy target volumes – perspective

Different types of imaging

- functional imaging with novel amino acid PET radiotracers, in particular, [11C]-Methionine (MET) PET has been correlated with areas at risk of disease progression to guide planning;
- [18F]-Fluoroethyltyrosine (FET)-based target volume delineation has been used to augment volumes defined with anatomic MRI alone, with no documented marginal or distant failures

3 different advanced imaging strategies seeking to redefine target delineation for glioblastoma:

- multiparametric magnetic resonance (MR),
- MR spectroscopy
- functional imaging

trials are currently under way to compare FET-PET with MRI alone in randomized settings (NCT01252459

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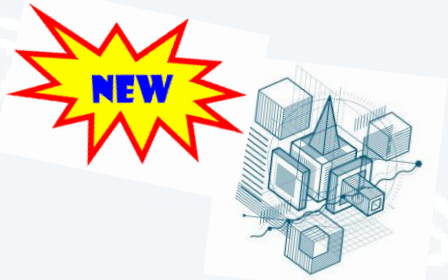
Primary tumors Radiotherapy target volumes – MRI



This study quantifies interfraction dynamics (tumor size, position, and geometry) based on sequential MR imaging scans obtained during standard 6-week chemoradiation

MR gadolinium-enhanced T1 (T1c) and T2/FLAIR axial sequences at planning (Fx0),
fraction 10 (Fx10),
fraction 20 (Fx20),
and 1 month after the end

Target dynamics were quantified by absolute volume (V), volume relative to Fx0 (Vrel), and the migration distance (dmigrate; the linear displacement of the GTV or CTV relative to Fx0).

Clinical Investigation

Quantitating Interfraction Target Dynamics During Concurrent Chemoradiation for Glioblastoma: A Prospective Serial Imaging Study

Int J Radiation Oncol Biol Phys, Vol. 109, No. 3, pp. 736e746, 2021

Primary tumors

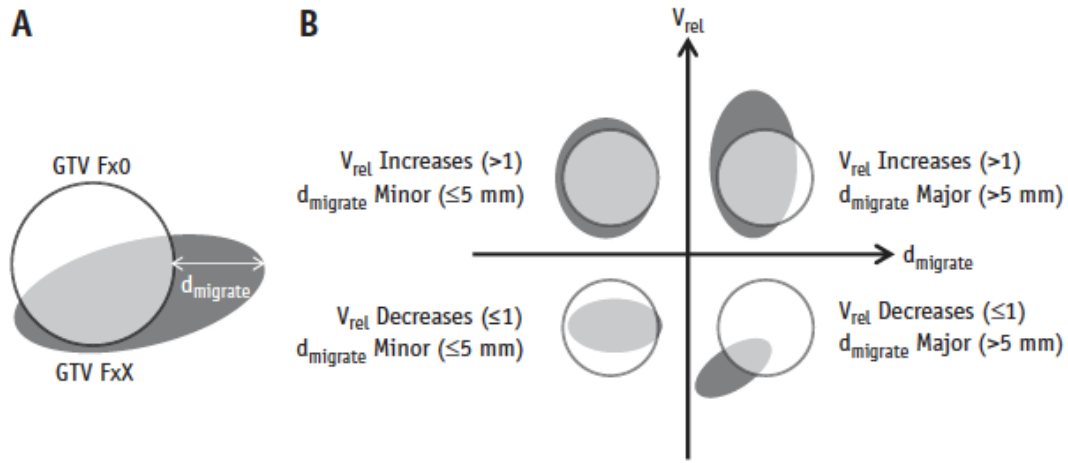


Fig. 1. (A) Schematic illustration of the migration distance ($d_{migrate}$). The migration distance is the maximum linear distance (in 3 dimensions) the target—either the gross tumor volume (GTV) or the clinical target volume (CTV)—deviates from its original radiation therapy planning (Fx0) volume. In the illustration, the GTV at planning (Fx0; unfilled circle) and the GTV at a later time point (FxX; shaded ellipse) are depicted. (B) Combining minor ($d_{migrate}$ ≤5 mm) and major ($d_{migrate}$ >5 mm) migration distances with decreasing (volume relative to Fx0 [V_{rel}] ≤1) and increasing (V_{rel} >1) relative target volumes yields 4 distinct combinations, as illustrated.

Clinical Investigation

Quantitating Interfraction Target Dynamics During Concurrent Chemoradiation for Glioblastoma: A Prospective Serial Imaging Study

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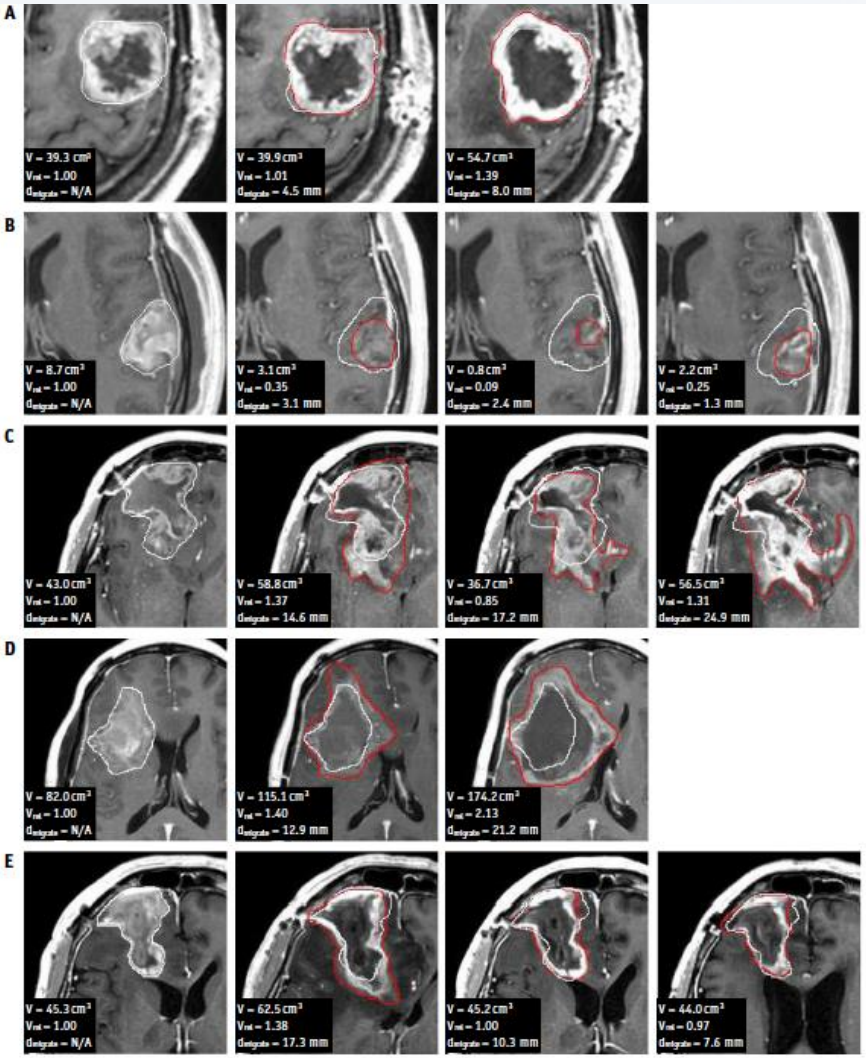

- The GTV (CTV) migration distances were greater than 5 mm in 46% (54%) of patients at Fx10, 50% (58%) of patients at Fx20, and 52% (57%) of patients at P1M.

- with 40% of patients exhibiting a decreased GTV (Vrel1) with a dmigrate >5 mm during chemoradiation therapy.

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Primary tumors

Clinical implication

- The attention to target volume is guided by → analysis of recurrence
  → treatment related toxicity
  → peritumoral at risk volume

- Extensive margin GTV_CTV (1.5-2 cm) → include the majority of intrafraction tumour dynamic change

Clinical Investigation

Quantitating Interfraction Target Dynamics During Concurrent Chemoradiation for Glioblastoma: A Prospective Serial Imaging Study

Int J Radiation Oncol Biol Phys, Vol. 109, No. 3, pp. 736e746, 2021

Primary tumors

Clinical implication

1) 58% and 68% of patients had a Dmigrate >5 mm for the GTV and CTV suggests that with a trend toward a decrease in the GTV and CTV, an isotropic margin of 3 to 5 mm for PTV is insufficient to accommodate inter-fraction tumour dynamics

2) GTV and CTV dynamics are correlated, strategies to adapt to changes in GTV morphology during RT will translate to improved coverage of the CTV. Given that the predominant pattern of volume change was a reduction in the GTV and CTV and that the majority experience a decreasing Vrel, the therapeutic impact of adaptive radiation therapy as the GTV shrinks → reduction in the volume of brain irradiated.

3) the majority of target changes occur between Fx0 and Fx10; Between Fx0 and Fx10, absolute T1c GTV changed by a range of 33.2 to 33.2 cm3. Similarly, the GTV and CTV migration distance was as large as 17.3 and 16.2 mm, respectively.

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Quantitating Interfraction Target Dynamics During Concurrent Chemoradiation for Glioblastoma: A Prospective Serial Imaging Study

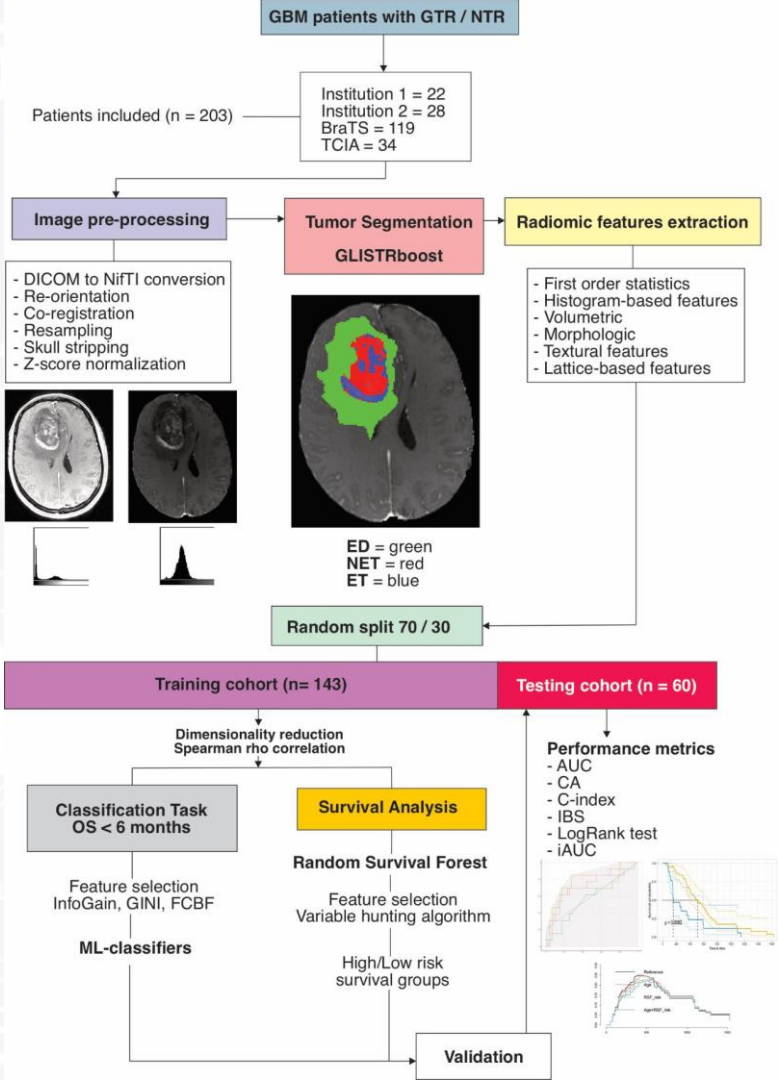
Int J Radiation Oncol Biol Phys, Vol. 109, No. 3, pp. 736e746, 2021

Primary tumors

NEW

Imaging and radiomics and AI

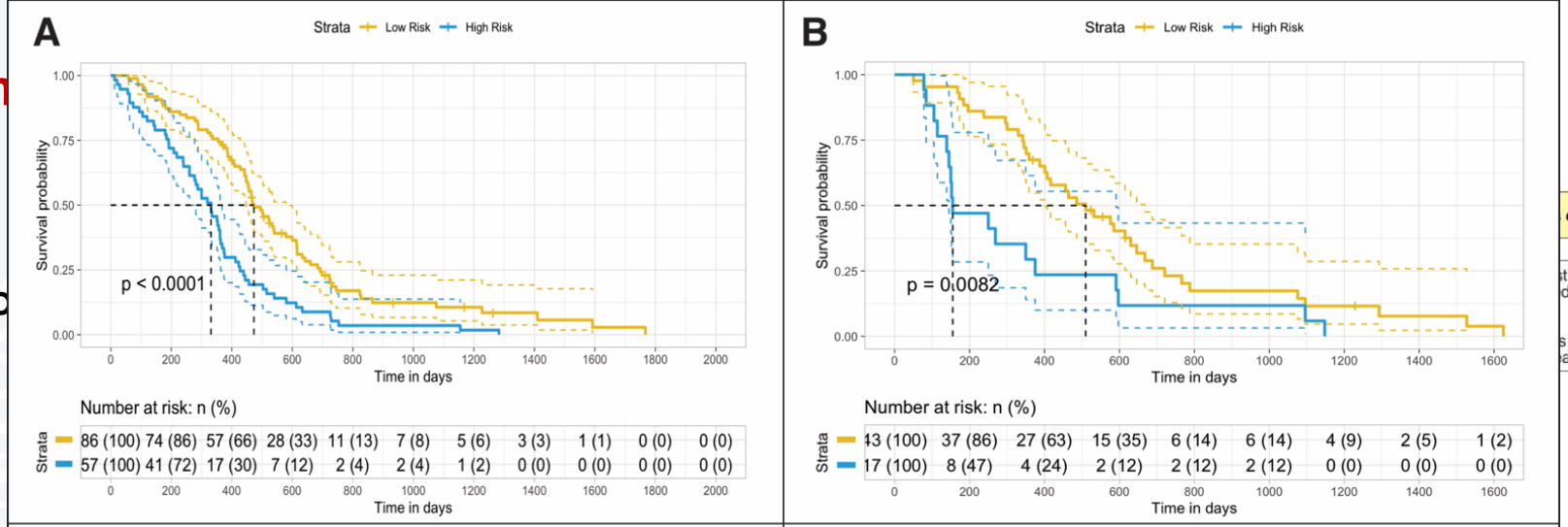
- Radiomics characteristics and prediction of survival



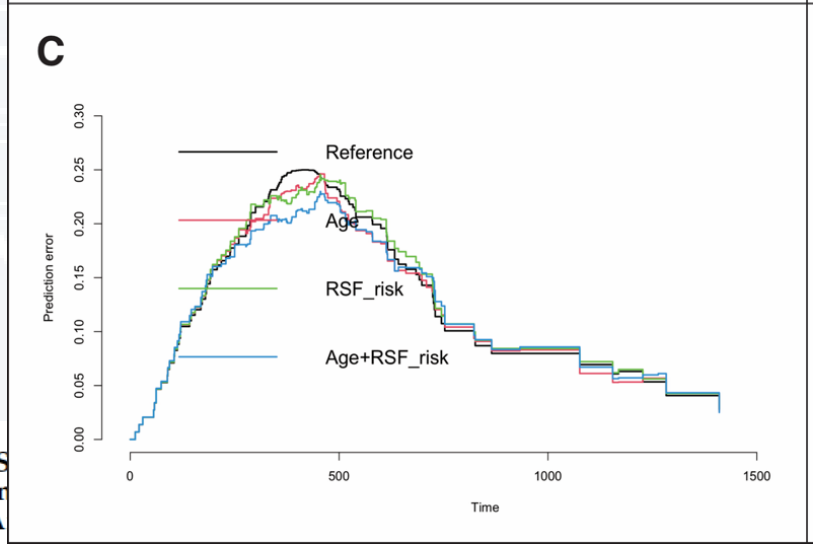
Article

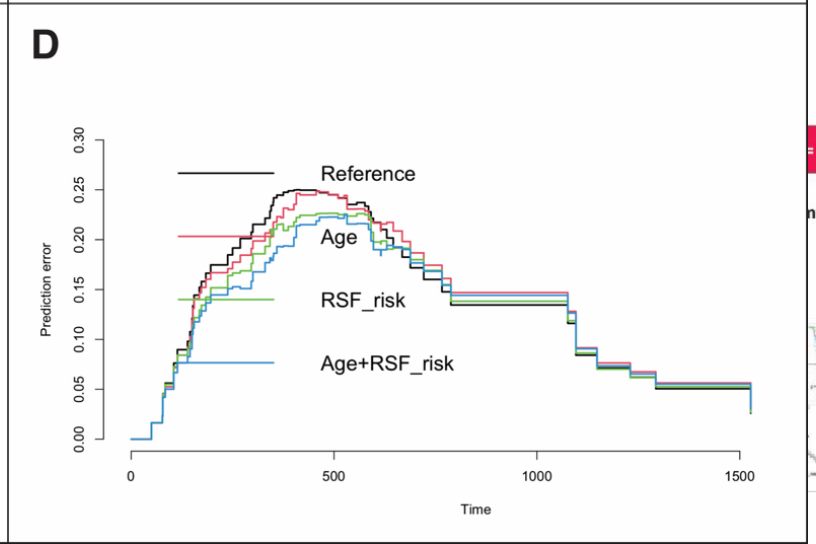
Predicting Short-Term Survival after Gross Total or Near Total Resection in Glioblastomas by Machine Learning-Based Radiomic Analysis of Preoperative MRI

Cancers 2021, 13, 5047


A
Strata
Low Risk
High Risk
Survival probability
p < 0.0001
Time in days
Number at risk: n (%)
Strata
86 (100) 74 (86) 57 (66) 28 (33) 11 (13) 7 (8) 5 (6) 3 (3) 1 (1) 0 (0) 0 (0)
57 (100) 41 (72) 17 (30) 7 (12) 2 (4) 2 (4) 1 (2) 0 (0) 0 (0) 0 (0) 0 (0)
Time in days

B
Strata
Low Risk
High Risk
Survival probability
p = 0.0082
Time in days
Number at risk: n (%)
Strata
43 (100) 37 (86) 27 (63) 15 (35) 6 (14) 6 (14) 4 (9) 2 (5) 1 (2)
17 (100) 8 (47) 4 (24) 2 (12) 2 (12) 2 (12) 0 (0) 0 (0) 0 (0)
Time in days


C
Prediction error
Reference
Age
RSF_risk
Age+RSF_risk
Time

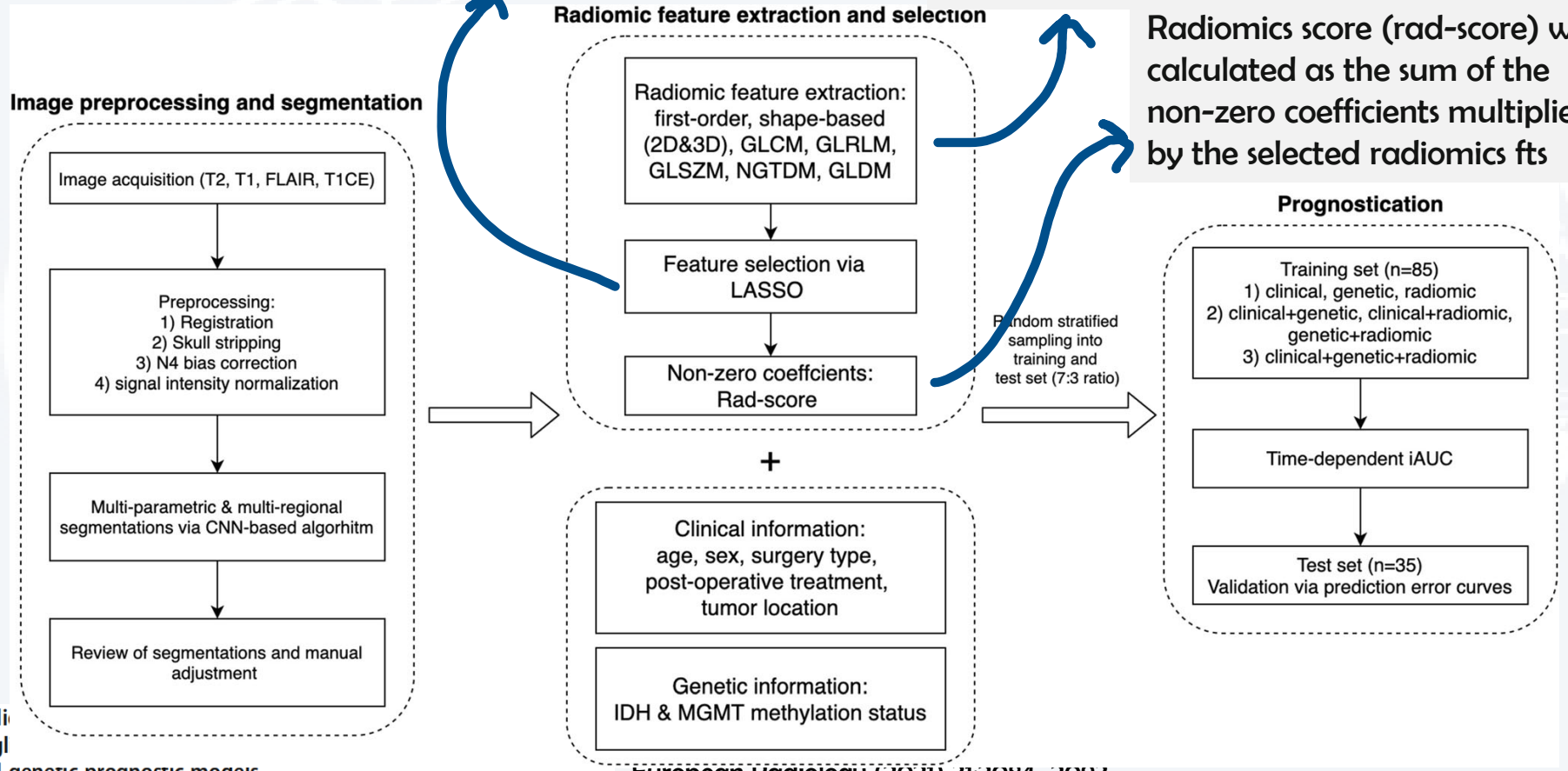

D
Prediction error
Reference
Age
RSF_risk
Age+RSF_risk
Time

Primary tumors

Resulted in 13 and 17 features associated with OS and PFS

The optimal threshold, according to survival differences, yielded 187 and 122 features for OS and PFS

Radiomics score (rad-score) was calculated as the sum of the non-zero coefficients multiplied by the selected radiomics fts



Radi
in gl
and genetic prognostic models

European Radiology (2021) 31:2084–2093

Primary tumor

Table 3 Multivariate analysis of Cox proportional hazards for overall and recurrence-free survival

Model | Overall survival | Progression-free survival

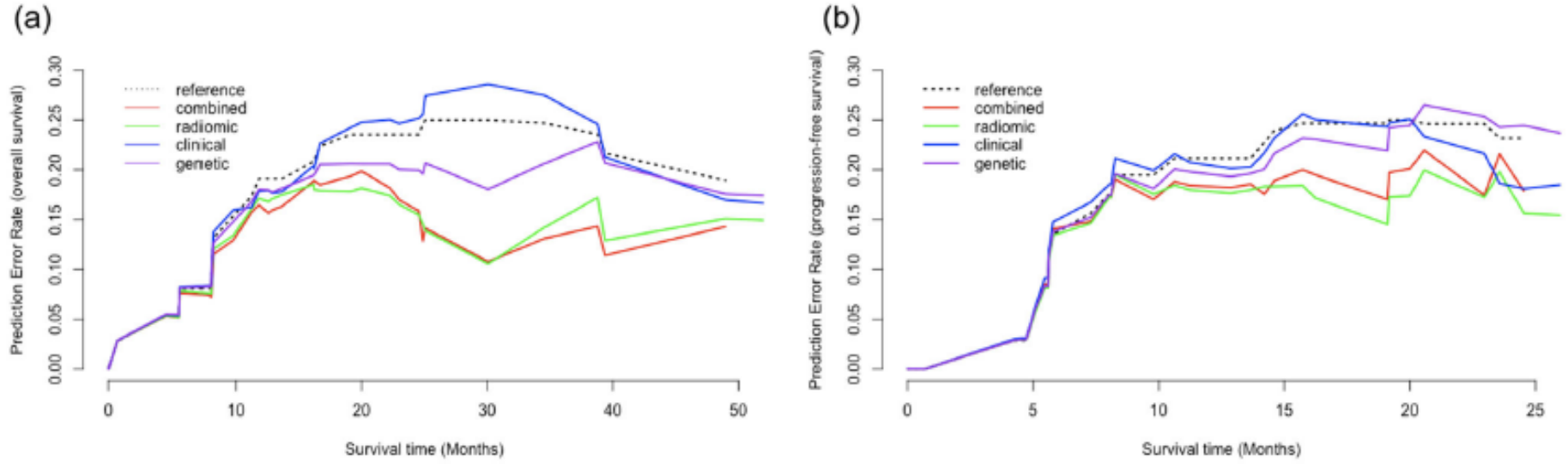


Fig. 5 Predictor error curves of multivariate Cox models for (a) overall survival and (b) progressionfree survival

[1] Includes age, sex, surgery type, tumor location, and post-operative treatment

[2] Includes IDH mutation and MGMT methylation status

[3] Includes weighted rad-score calculated from selected radiomic features

Rad
in glioblastoma patients when combined with conventional clinical and genetic prognostic models

European Radiology (2021) 31:2084–2093

Primary tumors

NEW

Radiotherapy and doses

Standard dose → 60 Gy in 30#
→ 40.05 in 15#

- A total of 26 reports (prospective) were included in the qualitative portion of the systematic review and 22/26 articles utilized for quantitative meta-analysis.
- Comparison DeRT vs SoC-RT with/out TMZ
- both a PFS and OS benefit to patients with DeRT alone vs SoC-RT alone
- neither a PFS nor an OS benefit was found with DeRT + TMZ vs SoC-RT + RT


Journal Pre-proof

Dose Escalated Radiotherapy for Glioblastoma Multiforme: An International Systematic Review and Meta-Analysis of 22 Prospective Trials

Raj Singh M.D. , Eric J. Lehrer M.D., M.S. , Ming Wang M.S., Ph.D. , Haley K. Perlow MD. , Nicholas G. Zaorsky MD MS , Daniel M. Trifiletti M.D. , Joseph Bovi M.D. , Pierina Navarria MD , Silvia Scoccianti MD , Vinai Gondi M.D. , Paul D. Brown M.D. , Joshua D. Palmer M.D.

PII: S0360-3016(21)00488-0
DOI: https://doi.org/10.1016/j.ijrobp.2021.05.001
Reference: ROB 27055

Primary tumors

NEW

Neuro-Oncology
23(3), 447–456, 2021 | doi:10.1093/neuonc/noaa165 | Advance Access date 13 July 2020

Pulsed radiation therapy for the treatment of newly diagnosed glioblastoma

- Pulsed RT (PRT), also referred to as low-dose rate therapy, divides 2-Gy fraction into ten 0.2-Gy pulses, separated by 3-minute intervals.

- PRT may bypass the limitations of SRT and has proven to be efficacious in preclinical studies.
- PRT, while enhancing tumor kill, may also enhance the therapeutic index as it allows more time for repair of RT-induced damage within non-dividing normal cells compared with SRT

This is a single-arm, prospective study.

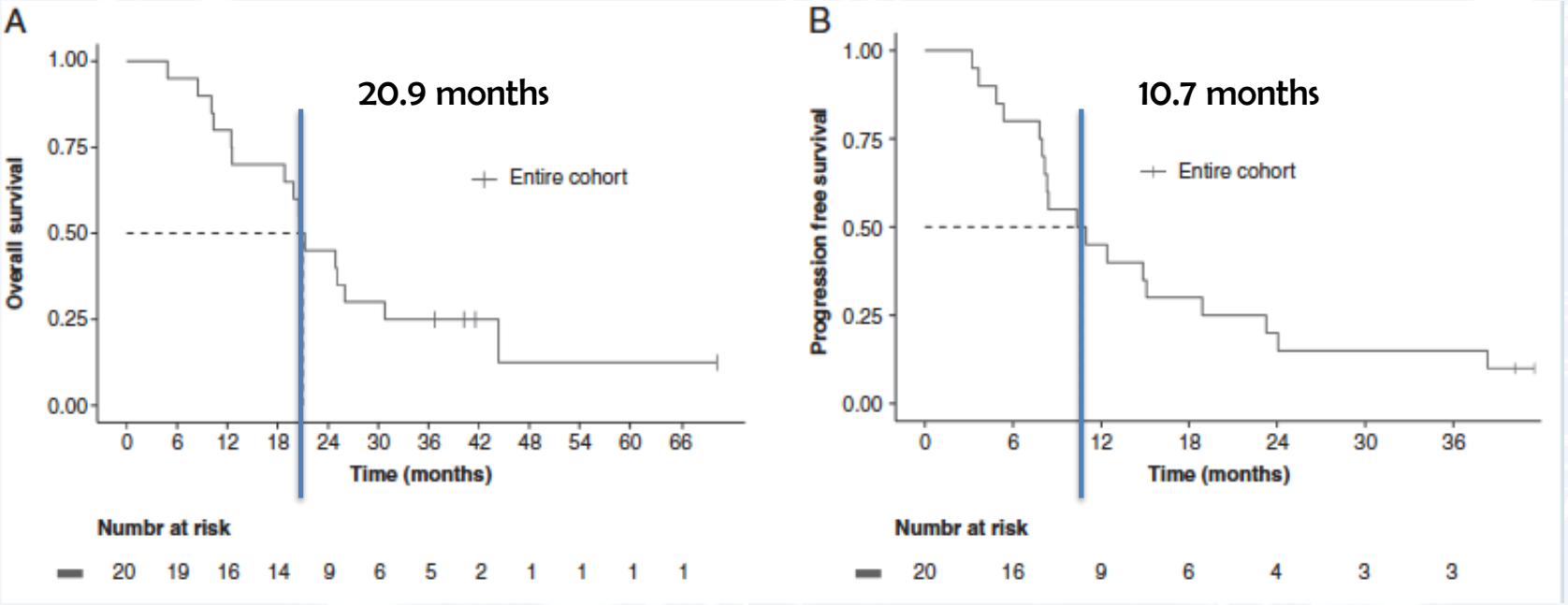
Patients received 60 Gy PRT utilizing VMAT/ single arc.
PRT was delivered in daily 2-Gy fractions, given in ten 0.2-Gy pulses; separated by 3-minute "beam-off" intervals → 40 min daily treatment

Primary tumors

Neuro-Oncology
23(3), 447–456, 2021 | doi:10.1093/neuonc/noaa165 | Advance Access date 13 July 2020

Pulsed radiation therapy for the treatment of newly diagnosed glioblastoma

21 patients



Primary tumors

Neuro-Oncology
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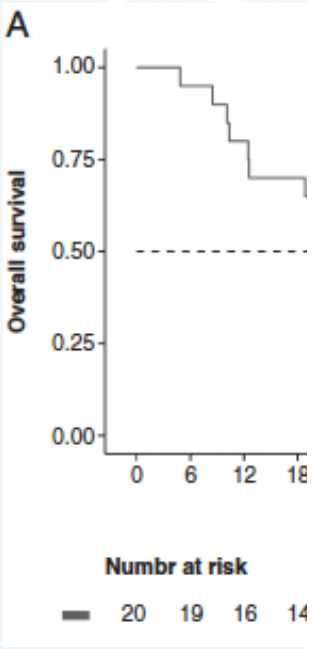
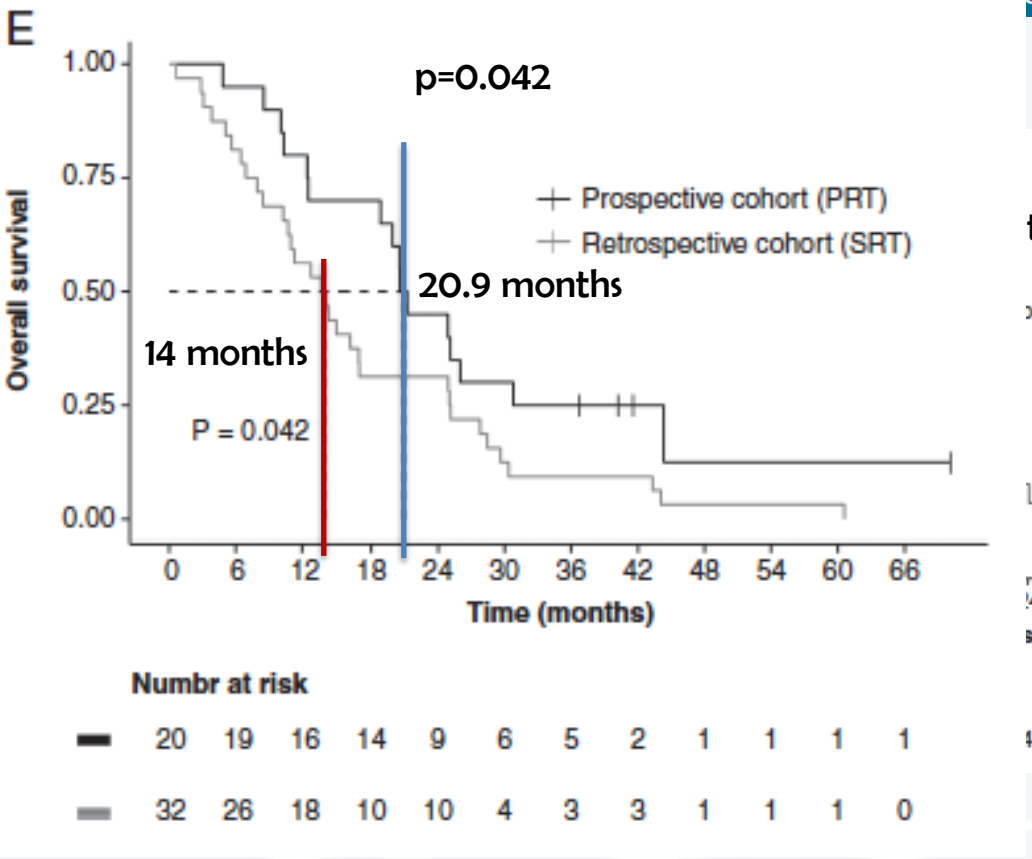
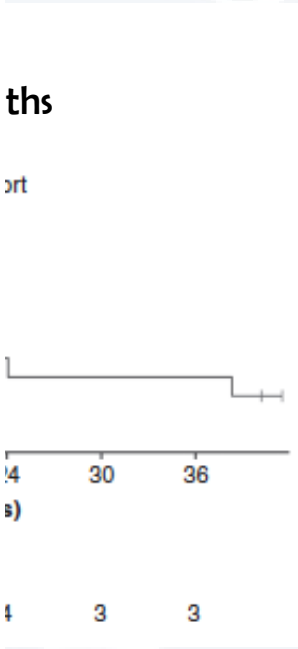
Pulsed radiation therapy for the treatment of newly
oblastoma

21 patients







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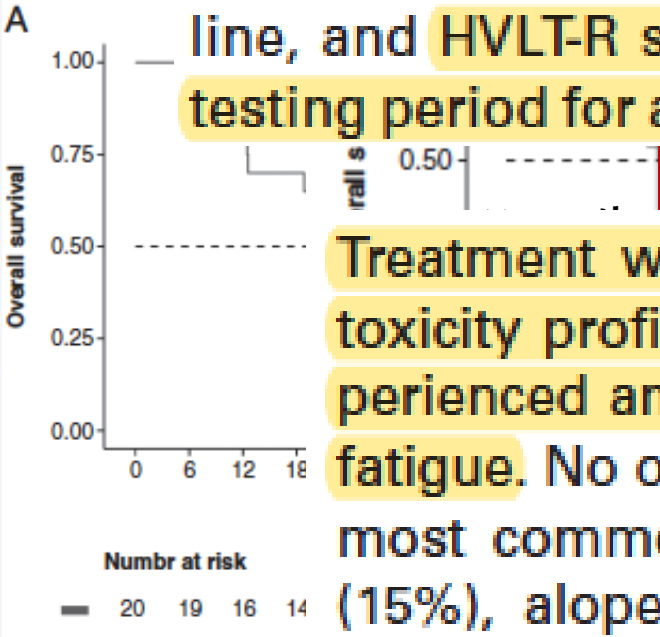
Prim

ent of newly

21 patie

There was no significant deterioration in any of the HVLT-R scores. Additionally, we calculated change in score from each time point to baseline, and HVLT-R scores remained stable throughout the testing period for all eligible patients. The average change



Treatment with PRT was well tolerated with a favorable toxicity profile, Only one patient experienced an acute grade 3 RT-related toxicity, which was fatigue. No other acute grade 3+ toxicities were noted. The most common acute grade 2 toxicities included nausea (15%), alopecia (15%), and cognitive disturbance (15%). There were no chronic grade 3+ RT-related adverse events.

Primary tumors

Neuro-Oncology
23(3), 345–346, 2021 | doi:10.1093/neuonc/noab008 | Advance Access date 22 February 2021

Reimagining external beam radiotherapy for glioblastoma: "old beam, new trick"

injury mitigation is of concern. Because pulsed radiation therapy as described in this current manuscript does not require new authorizations or regulatory approvals, the economic benefits of this strategy that would make it more accessible and feasible to a greater population worldwide, with greater efficiency in speed of availability. While the potential for increased daily treatment time from pulsed techniques or from repeated setup verification may deter busier centers from employing such approaches, the ability to develop strategies with existing technologies may be especially appealing to radiation oncologists who have patient bases willing and appropriate for trials, but lack the access to perform research using more expensive therapies.

Primary tumors

Radiotherapy - technique

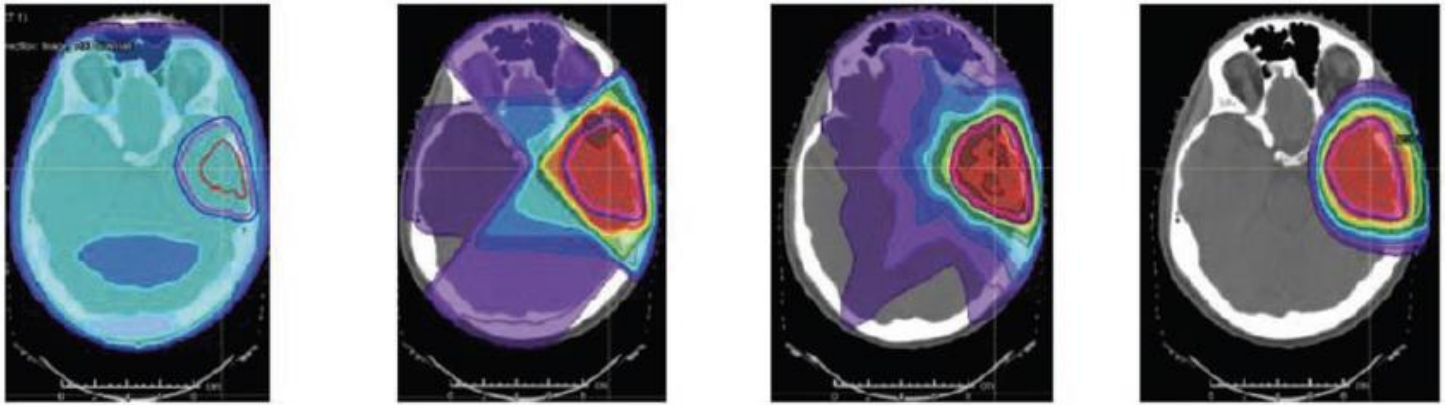


Fig. 9 This figure shows, from left to right, how the transition from 2D RT to 3D RT to intensity modulated radiotherapy to intensity modulated proton therapy harnesses the potential for sparing normal, uninvolved brain substructures from unnecessary RT dose; whether this produces meaningful patient clinical benefit is a subject of current clinical trial testing.

Neuro-Oncology
22(8), 1073–1113, 2020 | doi:10.1093/neuonc/noaa106 | Advance Access date 24 April 2020

Primary tumors

NEW

Radiotherapy – technique – temptations to increase RT efficacy

Radiosurgery

- Stereotactic radiosurgery (SRS) allows spatially precise targeted delivery of high-dose radiation with sub-millimeter accuracy.
- It is commonly used for treatment of small-to-moderate volume discrete brain lesions residing in deeper and/or functionally eloquent brain regions

Recurrent GBL

- Small volumes
- Small margin
- Limited fractions

Primary GBL → boost

- Small volumes
- Small margin
- Higher dose

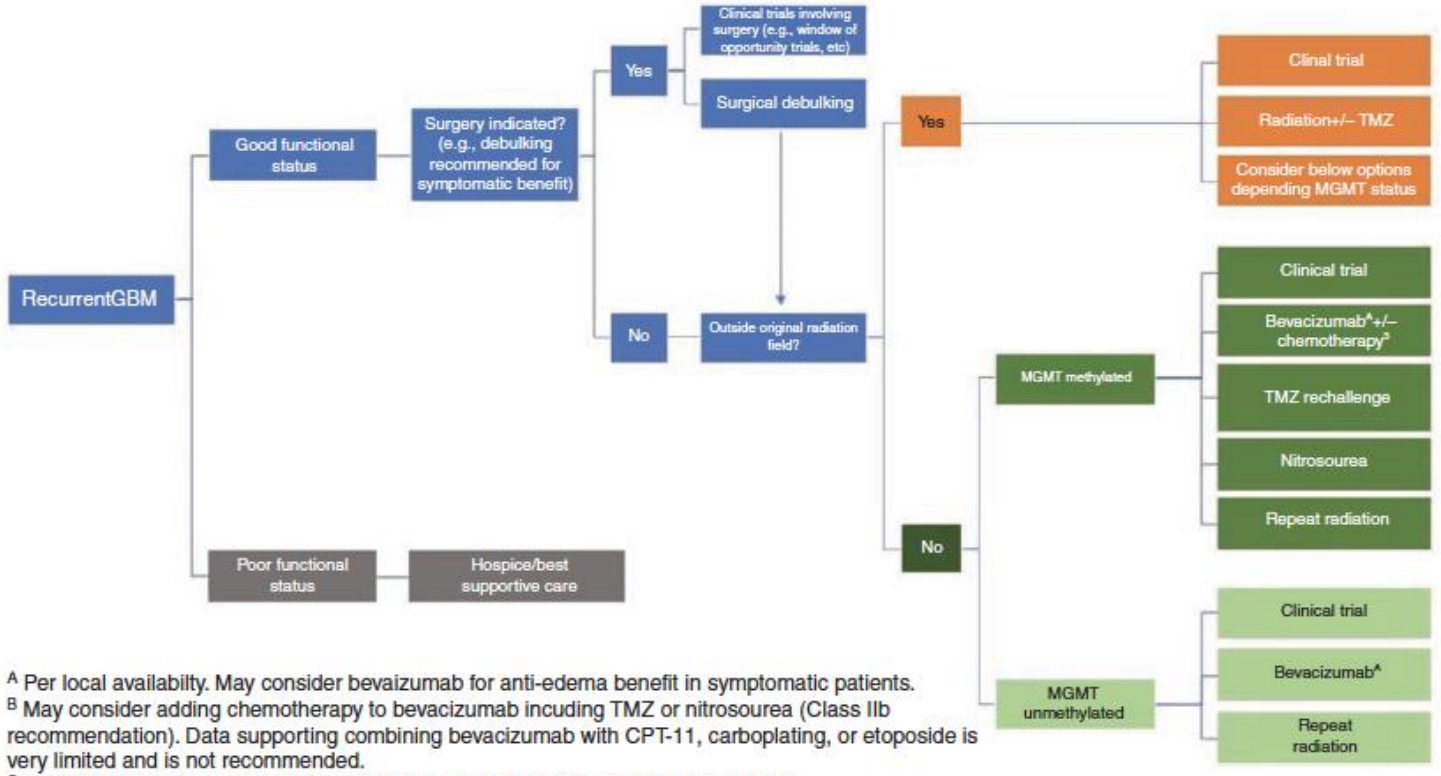
- RTOG 93–05 ® SRS boost delivered upfront of FRT ·
- 203 patients v tumor → NEG

- Different retrospective studies → SRS as sequential boost → POS

32. Kong D-S, Kim Y-H, Kim YH, et al. Long-term efficacy and tolerability of gamma knife radiosurgery for growth hormone-secreting adenoma: a retrospective multicenter study (MERGE-001). World Neurosurg 2019;122:e1291–9.
33. Shrieve DC, Alexander E, Black PM, et al. Treatment of patients with primary glioblastoma multiforme with standard postoperative radiotherapy and radiosurgical boost: prognostic factors and long-term outcome. J Neurosurg 1999;90(1):72–7.
34. Nwokedi Emmanuel C, DiBiase Steven J, Jabbour Salma, et al. Gamma knife stereotactic radiosurgery for patients with glioblastoma multiforme. Neurosurgery 2002;50(1):41–6 [discussion: 46–7].
35. Hsieh Patrick C, Chandler James P, Sandeep B, et al. Adjuvant gamma knife stereotactic radiosurgery at the time of tumor progression potentially improves survival for patients with glioblastoma multiforme. Neurosurgery 2005;57(4):684–92 [discussion: 684–92].

Primary tumors

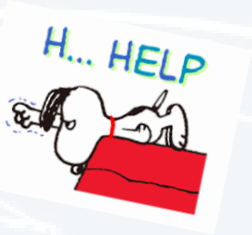
Standard treatment at recurrence



[A] Per local availabilty. May consider bevaizumab for anti-edema benefit in symptomatic patients.
[B] May consider adding chemotherapy to bevacizumab incuding TMZ or nitrosourea (Class IIb recommendation). Data supporting combining bevacizumab with CPT-11, carboplating, or etoposide is very limited and is not recommended.
[C] The optimal treatment-free interval prior to pursuing TMZ rechallenge is unknown.

Neuro-Oncology
22(8), 1073–1113, 2020 | doi:10.1093/neuonc/noaa106 | Advance Access date 24 April 2020

Primary tumors – recurrence



Temozolomide Rechallenge

Rechallenge with TMZ may be reasonable, especially in patients with *MGMT* promoter methylated glioblastoma that relapses more than a few months after completion of maintenance TMZ in the first-line setting.[149,150] The uncontrolled RESCUE study observed that patients who lived longest with dose-dense TMZ were those who progressed after a treatment-free interval.[149] While *MGMT* status was not predictive of outcome in the RESCUE study, the DIRECTOR trial did demonstrate increased time to treatment failure with TMZ rechallenge in patients with *MGMT* promoter methylated versus unmethylated tumors.[150] However, there is no evidence to suggest that TMZ rechallenge is superior to nitrosoureas in any patient population.

Neuro-Oncology
22(8), 1073–1113, 2020 | doi:10.1093/neuonc/noaa106 | Advance Access date 24 April 2020

Primary tumors – recurrence

Nitrosoureas

Nitrosoureas, including lomustine, carmustine, and fotemustine, have good blood–brain barrier (BBB) penetration.[189] Fotemustine is available in some European countries, but has not been approved for use in the United States. Lomustine is generally preferred over carmustine given its oral formulation, schedule of administration, and better safety profile. In several phase III randomized trials, the lomustine monotherapy arm (dosed as 6 wk cycles of 100–130 mg/m^2 for up to 6 cycles) was associated with median OS of 7.1–8.6 months and PFS of 1.5–3 months.[148,190] Data from these trials also suggest that patients with *MGMT*-methylated tumors are more likely to benefit from nitrosoureas than those with unmethylated *MGMT*.[148,191,192]

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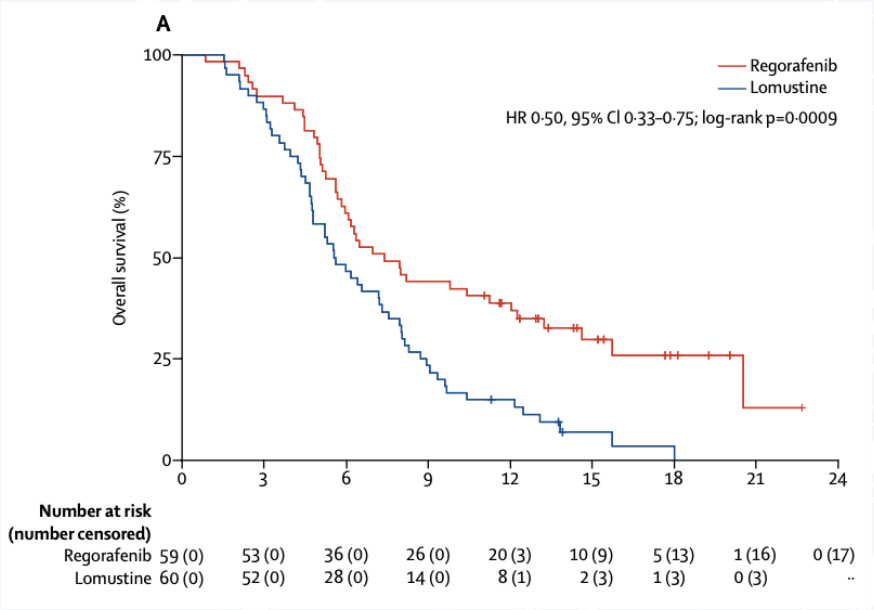
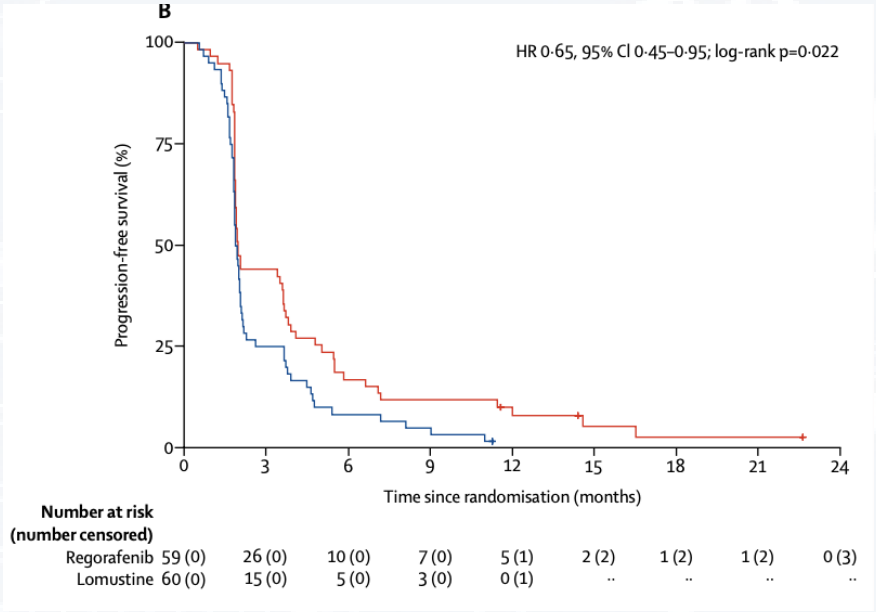
Primary tumors – recurrence

Regorafenib





Lancet Oncol 2019; 20: 110–119

Primary tumors – recurrence

Radiotherapy – reirradiation (RI)

Relevant clnical questions

- the appropriate patient selection
- radiation technique
- optimal dose fractionation
- reirradiation tolerance of the brain and
- the risk of radiation necrosis.

Target definition

GTV → the visible lesion on MRI contrast-enhanced T1; CTV→ potential suspected microscopic tumor infiltration and potential paths of microscopic spread, is adding a variable margin of 0–5 mm to the GTV
- PET/CT with radiolabeled aa may help

Brain toxicity

- For conventional fractionation (2Gy/#), 5%-10% risk of symptomatic RN → (BED) of 72 Gy (range, 60–84 Gy) - 90 Gy (range 84–102 Gy)
- SRS, the risk increases rapidly → brain to 12 Gy is >5–10 ml
- In RI → consider: dose, fractionation, treated volume, combined CHT, and interval between radiation treatments
- No RN if BED EqD2 cumulative < 96 Gy
- risk → 0–3% after conventional fractionation at cumulative EQD2 < 101 Gy; → 7–13% after hypoSRT at cumulative EQD2 of 102–130 Gy; →and up to 24.4% after SRS cumulative EQD2 of 124–150 Gy

Current status and recent advances in reirradiation of glioblastoma

Radiat Oncol (2021) 16:36

Primary tumors – recurrence

Radiotherapy – reirradiation (RI)

Survival benefit

SRS →

- 15-18 Gy volume 4-10 ml → PFS 4.4-6 mo; OS 7.5-13 mo
- SRS + TMZ → slightly better
- Risk of RN is related to dose and volume (value around 120 Gy risk <10% when volume <10ml)

Hypo →

- 30-45 Gy in 2.5-4Gy/# → 7.5-12.5 mo
- Association with TMZ can improve results

Conventional →

- 36 Gy in 18 # → PFS 2.5-5 mo; OS 6.7-
- RN risk is low also in volumes 100 ml o

Prognostic factors

- age; KPS; histology are confirmed as prognostic factors
- salvage surgery before reirradiation and the time between radiation courses did not emerge as ind ent

reirradiation has emerged as an effective and safe treatment option for selected patients with recurrent GBM.

Current status and recent advances in reirradiation of glioblastoma

Radiat Oncol (2021) 16:36

Prima

Radiothera

Table 2 Clinical trials involving ICB with radiation

Clinical trial identifier	Phase	Name of trial	Primary/recurrent	N	Cohort(s)	Treatment arms	Primary endpoint	Status/conclusion
NCT02617589 (CheckMate 498) [61]	III	An investigational immuno-therapy study of nivolumab compared to temozolomide, each given with radiation therapy, for newly-diagnosed patients with glioblastoma (GBM, a malignant brain cancer) (CheckMate 498)	Primary	550	N/A	1. Nivolumab + radiotherapy 2. Temozolomide + radiotherapy	Overall survival (3 years)	Recruiting; primary endpoint not met–overall survival
NCT02667587 (CheckMate 548) [62]	III	An investigational immuno-therapy study of temozolomide plus radiation therapy with nivolumab or placebo, for newly diagnosed patients with glioblastoma (GBM, a malignant brain cancer) (CheckMate548)	Primary	693	N/A	1. Nivolumab + temozolomide + Radiotherapy 2. Nivolumab placebo + temozolomide + Radiotherapy	1. Overall survival (24 months) 2. Progression free survival (35 months)	PFS not met; continual evaluation of OS
NCT03743662	II	Nivolumab with radiation therapy and bevacizumab for recurrent MGMT methylated glioblastoma	Recurrent	94	1. Patients with recurrent GBM not undergoing surgical debulking as part of their treatment plan 2. Patients with recurrent GBM who are undergoing surgery as part of their treatment	1. Nivolumab followed by re-radiation + bevacizumab (if deemed beneficial) 2. Nivolumab followed by re-resection, then re-radiation + bevacizumab (if deemed beneficial)	Overall survival (2 years)	Recruiting; primary endpoint not met
NCT03661723	II	Pembrolizumab and Reirradiation in bevacizumab naïve and bevacizumab resistant recurrent glioblastoma	Recurrent	60	1. Bevacizumab naïve 2. Bevacizumab recurrent	1. Pembrolizumab + re-Irradiation (lead-in) 2. Pembrolizumab + bevacizumab + re-irradiation (lead-in) 3. Pembrolizumab + re-irradiation 4. Pembrolizumab + bevacizumab + re-irradiation	Objective response rate (2 years) Overall survival (12 months)	Recruiting

Table 2 (continued)

Clinical trial identifier	Phase	Name of trial	Primary/recurrent	N	Cohort(s)	Treatment arms	Primary endpoint	Status/conclusion
NCT03367715	II	Nivolumab, ipilimumab, and short-course radiotherapy in adults with newly diagnosed, MGMT unmethylated glioblastoma	Primary	24	N/A	Single arm: Nivolumab + Ipilimumab + short-course radiation	Overall survival (1 year)	Not yet recruiting
NCT03018288	II	Radiation therapy plus temozolomide and pembrolizumab with and without HSPPC-96 in newly diagnosed glioblastoma (GBM)	Primary	108	N/A	1. Radiotherapy + temozolomide + pembrolizumab 2. Radiotherapy + temozolomide + HSPPC-96 vaccine 3. Radiotherapy + temozolomide + placebo	Overall survival (1 year)	Recruiting
NCT03174197	II/I	Atezolizumab in combination with temozolomide and radiation therapy in treating patients with newly diagnosed glioblastoma	Primary	60	One cohort, Phase I followed by Phase II	1. Phase II: concurrent Atezolizumab + temozolomide + radiotherapy 2. Phase I: Adjuvant atezolizumab + temozolomide	Phase II: overall survival (3 years) Phase I: Dose-limiting toxicities (10 weeks) Phase I + II: incidence of adverse events (3 years)	Recruiting
NCT02052648 [63, 64]	II/I	Study of the IDO pathway inhibitor, indoximod, and temozolomide for pediatric patients with progressive primary malignant brain tumors	Primary	160	1. Bevacizumab-naïve patients 2. Patients receiving of have received and failed Bevacizumab 3. Patients who will receive stereotactic radiosurgery	Phase Ib Single arm: indoximod (dose escalation) + temozolomide Phase II Single arm: Indoximod + temozolomide (dosed at 150–200 mg/m2) cohort 1, 2,3	Phase I: Determine Phase 2 dosing Phase II: Efficacy (18 month)	Recruitment completed; indoximod MTD: 1200 mg BID
NCT04047706	I	Nivolumab, BMS-986205, and radiation therapy with or without temozolomide in treating patients with newly diagnosed glioblastoma	Primary	30	1. Patients with MGMT methylated promoter 2. Patients with MGMT unmethylated promoter	1. Radiation + temozolomide + BMS-986205 (anti-IDO1) + nivolumab (Cohort I) 2. Radiation + BMS-986205 (anti-IDO1) + nivolumab (cohort II)	Incidence of adverse events (up to 30 days after last dose)	Recruiting

Table 2 (continued)

Clinical trial identifier	Phase	Name of trial	Primary/recurrent	N	Cohort(s)	Treatment arms	Primary endpoint	Status/conclusion
NCT03426891 [65]	I	Pembrolizumab and vorinostat combined with temozolomide for newly diagnosed glioblastoma	Primary	32	Part 1: Dose escalation of Vorinostat Part 2: Dose Expansion (All participants receiving same dose of Vorinostat, MTD determined by part 1	Single arm: Pembrolizumab + vorinostat + temozolomide + Radiotherapy	MTD (12 weeks)	Recruiting Completed enrollment to dose level 1 No dose liming adverse event observed Most common adverse event: thrombocytopenia and fatigue
NCT02287428 [17]	I	Personalized neoantigen cancer vaccine … plus … for pa… MGM… newly…	Primary	46	…	…	…nd tolerability …l: # patients …ast 10 action-…ides (2 years) …: # patients …itiate post …py vac- …py within …from date of …years)	Active, not recruiting "Individualized, multi-neo-epitope vaccines are feasible, safe and capable of generating systemic and intra-tumoral immune responses in GBM patients that appear to be abrogated by dex"
NCT03197506	II	Pembrolizu… standard … treating patients with glioblastoma				Single arm: Neoadjuvant pembrolizumab + adjuvant pembrolizumab + temozolomide + radiotherapy	1. Dose limiting toxicities (5 years) 2. Overall Survival (18 months) 3. Progression-free Survival (5 years) 4. Time to progression (5 years) 5. Time to treatment failure (5 years)	Recruiting

Compendium of clinical trials that included radiation as part of therapy with checkpoint inhibition. Radiation is thought to have both direct tumoricidal and immunogenic effects

- As such, there is need for caution in simply transposing treatment of other cancers to GBM
- GBM will require further studies that explore how it is different from others tumors, including the relatively increased representation of myeloid cells compared to T lymphocytes in the tumor site

Glioblastoma Clinical Trials: Current Landscape and Opportunities for Improvement

Table 1. Key characteristics of current adult gl
trials.

Characteristic	A
Median time on ClinicalTrials.gov, mo (range, IQR)	2
Status, *n* (%)	
Currently recruiting	1
Not yet recruiting	1
Phase, *n* (%)	
0/I	3
0/II	2
I	6
I/II	2
II	5
II/III	2
III	4
Not listed	2
Tumor type, *n* (%)	
Glioma-specific	1
Solid tumor trial with glioblastoma arm(s)	1
Type of therapy, *n* (%)	
Systemic	1
Radiotherapy	5
Systemic + radiotherapy	5
Neoadjuvant/window-of-opportunity cohort	3
Intracerebral delivery	1
Tumor-treating fields	1
Sponsor, *n* (%)	
Investigator/foundation/	
Industry	
Study centers, *n* (%)	
Single center	
Multicenter	
Median number of cer	
Disease setting, *n* (%)	
Newly diagnosed gliobl	
Specific for MGMT uni glioblastoma	
Recurrent glioblastoma	
Both newly diagnosed a glioblastoma	
Allows IDH-mutant gliobl	
Yes	
No	
Not specified	
Allowed for phase I, exclu	
Allows molecular glioblas c-IMPACT NOW, *n* (%)	
Yes	
No	
Not specified	
Not applicable	

(Contin

Table 1. Key characteristics of current adult glioblastoma clinical trials. (Cont'd)

Characteristic	All trials (*N* = 157)
Requires standard of care with 60-Gy radiation and temozolomide (as part of regimen for newly diagnosed trial, or as prior therapy for recurrent trial), *n* (%)	
Yes	84 (54%)
No	45 (29%)
Not specified	25 (16%)
Yes for new treatment, no for recurrence	2 (1%)
Excludes multifocal disease, *n* (%)	34 (22%)
Includes control arm, *n* (%)	18 (11)
Internal control arm	14 (9)
External control arm	4 (2)
Randomized trial, *n* (%)	28 (18)

Abbreviations: IQR, interquartile range; NCI, National Cancer Institute; *MGMT*, O(6)-methylguanine–DNA methyltransferase; IDH, isocitrate dehydrogenase; c-IMPACT NOW, Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy—Not Officially WHO.

Glioblastoma Clinical Trials: Current Landscape and Opportunities for Improvement

Far from the objective if.....

Table 1. Key characteristics of current adult gl… trials.

Characteristic	
Median time on Clinical… mo (range, IQR)	
Status, *n* (%)	
Currently recruiting	1…
Not yet recruiting	1…
Phase, *n* (%)	
0/I	3
0/II	
I	
I/II	
II	
II/III	
III	
Not listed	
Tumor type, *n* (%)	
Glioma-specific	
Solid tumor trial with glioblastoma arm(s)	1…
Type of therapy, *n* (%)	
Systemic	1…
Radiotherapy	5
Systemic + radiotherapy	5
Neoadjuvant/window-of-opportunity cohort	3
Intracerebral delivery	1…
Tumor-treating fields	1…
Sponsor, *n* (%)	
Investigator/founda…	
Multicenter	
Median number of cer…	
Disease setting, *n* (%)	
Newly diagnosed gliobl…	
Specific for MGMT uni… glioblastoma	
Allows molecular glioblas… c-IMPACT NOW, *n* (%)	
Yes	
No	
Not specified	
Not applicable	

(Continu…

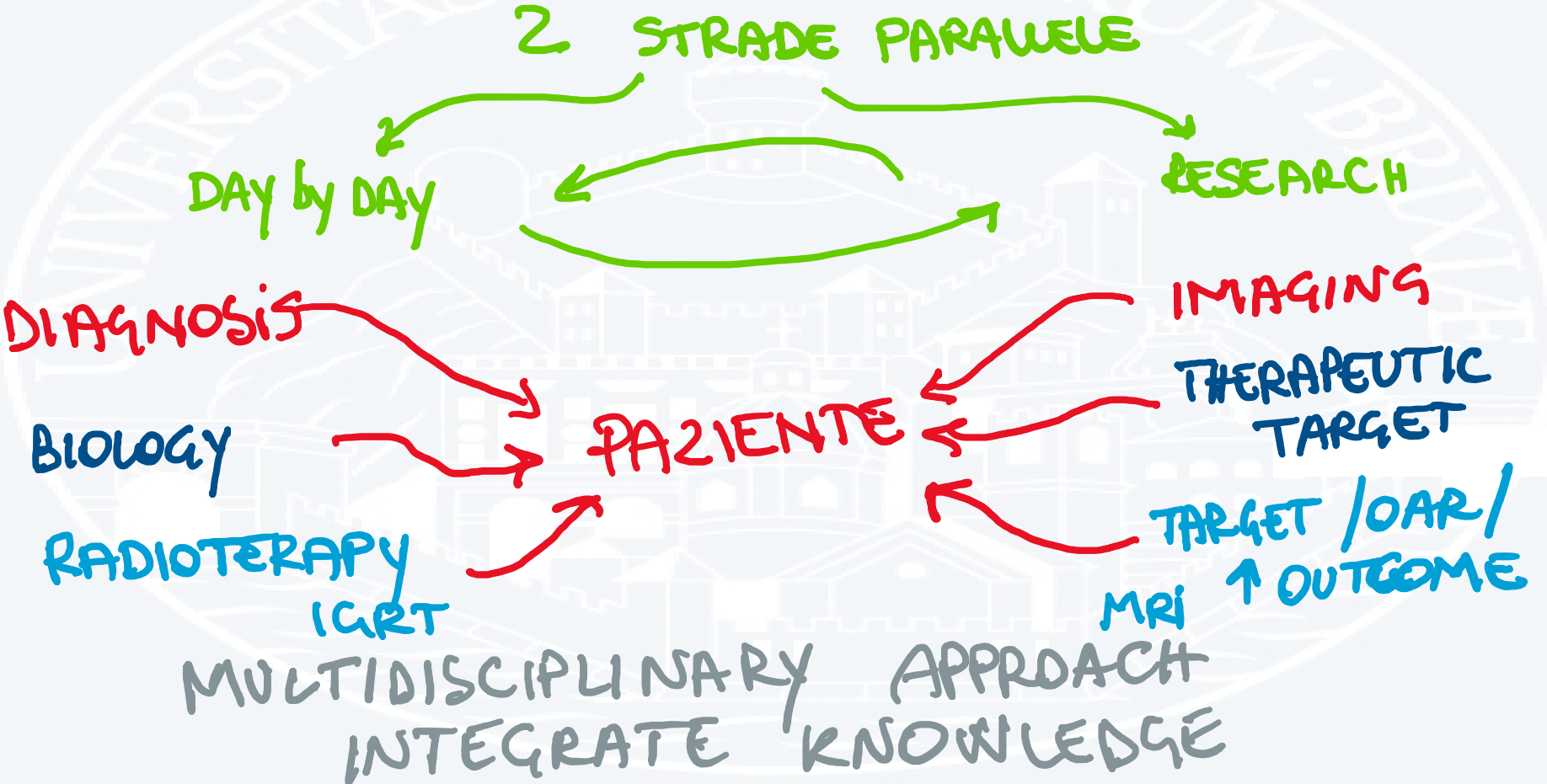
…haracteristics of current adult glioblastoma clinical …)

…teristic	All trials (*N* = 157)
Requires standard of care with 60-Gy radiation and temozolomide (as part of regimen for newly diagnosed trial, or as prior therapy for recurrent trial), *n* (%)	
External control arm	4 (2)
Randomized trial, *n* (%)	28 (18)

Abbreviations: IQR, interquartile range; NCI, National Cancer Institute; *MGMT*, O(6)-methylguanine–DNA methyltransferase; IDH, isocitrate dehydrogenase; c-IMPACT NOW, Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy—Not Officially WHO.

alizable results. In this review, we found that phase II glioblastoma trials continue to be conducted largely in single-center settings and with single-arm designs, placing the field at risk for continued late phase trial failures and beleaguered drug developme…

Primary tumors – conclusions – the winning strategy



Primary tumors

Radiotherapy and doses

Dose-Escalated Photon IMRT or Proton Beam Radiation Therapy Versus Standard-Dose Radiation Therapy and Temozolomide in Treating Patients With Newly Diagnosed Glioblastoma

ClinicalTrials.gov Identifier: NCT02179086

Screenshot

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

Recruitment Status : Recruiting
First Posted : July 1, 2014
Last Update Posted : November 5, 2021

See Contacts and Locations

Sponsor:
NRG Oncology

Collaborators:
National Cancer Institute (NC
Radiation Therapy Oncology

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	606 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	Randomized Phase II Trial of Hypofractionated Dose-Escalated Photon IMRT or Proton Beam Therapy Versus Conventional Photon Irradiation With Concomitant and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma
Actual Study Start Date :	October 27, 2014
Estimated Primary Completion Date :	May 2024
Estimated Study Completion Date :	May 2026